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The present study is designed to examine the relationships between hyperinsulinemia, insulin like growth factor-1, central adiposity, maximal adult weight, physical fitness and breast cancer risk in post-menopausal African-American women. The research design is a case-control study of women 55 to 79 years of age. Eligibility criteria for the cases will be newly histologically confirmed primary breast cancer. Both cases and controls will be identified during the same time frame and will come from the same population base. None of the controls will have a previous history of malignant or gynecological conditions that may have the same risk factors in breast cancer. Plasma levels of IGF-1 and insulin will be measured by radioimmunoassay. Central adiposity will be measured as waist-to-hip ratios (WHR). Multiple logistic regression will be used to determine age adjusted odds ratios for tertiles of waist, hip, WHR, maximal adult weight gain and levels of physical activity. Corresponding 95 percent confidence intervals will be based on the logistic regression models.

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FOREWORD

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N/A In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Tanya D Agnew-Collins 9/16/99

PI - Signature Date

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INTRODUCTION

The purpose of the study is to examine the relationships between central adiposity, maximum adult weight gain, physical fitness, hyperinsulinemia, insulin-like growth factors (IGF-1) and breast cancer risk. The majority of the studies that examined the relationship between breast cancer risk and weight used body mass index (BMI) as their measure for weight. However, BMI measures overall obesity and therefore may not be a sensitive indicator for breast cancer risk. Others have proposed that waist-to-hip ratios (WHR) are a more sensitive measure because it is closely related to the metabolic consequences of obesity such as alterations in ovarian hormones, fasting glucose metabolism and growth factors that have been shown to promote breast cancer cell growth. Several studies examined WHR's in postmenopausal women, but not with an African American population. Moreover, these studies did not determine whether WHR is associated with increased levels of IGF-1. Increased levels of insulin and IGF-I were found to be potent mitogens for the stimulation of growth in human breast cancer cells. Since WHR is believed to be associated with IGF- I through increased levels of insulin, it is important to document this relationship. Central adiposity, hyperinsulinemia and IGF- I may be biological markers for breast cancer risk.

Another lifestyle factor that effects breast cancer risk is time of weight gained and physical activity. Instead of measuring weight and physical activity at one point in time, it is more important to measure maximal adult weight gain and physical activity during that period of time when a women is undergoing hormonal change such as menarche, pregnancy and menopause. Timing of weight gain/change and physical activity with hormonal change is more relevance to risk for postmenopausal breast cancer. It may be possible to prevent or decrease breast cancer risk by maintaining a healthy weight and exercising more during the time of hormonal change. Specifically, this research is expected to show that central obesity is positively associated with increased levels of insulin, IGF-1 and risk for breast cancer. Additionally, we expect to show that increased levels of IGF-1 and maximal adult weight gain are positively associated with the risk for developing breast cancer and to determine the time period for the protective effect of physical activity with breast cancer risk.

BODY

Task 1 : Develop and finalize questionnaires for printing.

Study questionnaires were developed and finalized in February 1998.

Task 2: Hiring and Training Staff

After the grant was awarded August 15, 1997, the two positions along with the position descriptions for medical research assistant and data manager were approved by the University in October 1997. The positions were advertised and potential candidates were interviewed in November and December 1997. Two persons were selected and started working on the project in January and February 1998. In February, they were trained regarding study goals, objectives, protocols, responsibilities and how to finalize study questionnaires.

Task 3: Recruitment of cases and controls; informed consent; data collection

The research design is a case-control study of postmenopausal women who are 55 to 79 years of age. Initially, the sample size in the proposal was 50 cases and 50 control. However, after the revised budget was submitted, DOD asked me to respond to the study weakness cited by the reviewers. One of the cited study weaknesses was that the sample size was to small to detect a difference. In response to the reviewer's critic, the sample size was increased from 100 to 244 subjects. The increased is based on 80% power, alpha=0.05 and a relative risk of 2.0 for 122 cases and 122 controls (35). However, the original grant proposal and revised budget does not reflect this increase in sample size.

In February 1998, recruitment of patients started at the Howard University Mammography clinic and at the Georgetown Medical Center in October 1998. A prescreening questionnaire was developed and administered to potential participants to determine initial eligibility. After the patients met the prescreening criteria, they are given an appointment to determine final screening criteria. Once the patients are eligible, they participate in a (1) one-hour data collection interview.

From February 1998 through August 15, 1999, we have recruited 87 postmenopausal women without breast cancer who are serving as the control subjects and 30 postmenopausal women with breast cancer. To date we have enrolled 117 patients. The recruitment of women with breast cancer is slow. There are several reasons for this. First, the recruitment criteria eliminates persons who are diabetic and who are taking estrogen replacement therapy since the study is measuring insulin-like growth factor type-1 (IGF-1) and estradiol. In the African-American population, the prevalence of Type II diabetes is very high among women. It is becoming increasing difficult to find postmenopausal women who are not taking some form of estrogen replacement therapy. Also, we are finding a larger number of premenopausal black women with breast cancer when compared to postmenopausal black women at our institution. Therefore, expanding the recruitment database to include additional sites to recruit patients for the study is essential. We started recruiting patients from the Georgetown Medical Center in October 1998. Unfortunately, this institution did not have the number of minority patients that was predicted. In May 1999, I submitted a proposal to the DC General Hospital's Institutional Review Board, which has a large minority population-base. We will

start recruiting at this institution in October 1999. The addition of this site will increase the number of breast cancer patients for this project.

The PI sent a letter dated May 17, 1999, requesting a no-cost extension for one year to continue recruiting women into the study. Approval for the extension was granted in August 1999.

Task 4: Send Plasma to Laboratory for analysis; work with oncologist to determine primary breast cancer cases.

Plasma samples are drawn into tubes containing ethylene-diaminetetraaceticacid (ETA). The plasma is separated by centrifugation and analyzed by Quest Diagnostics, Inc., which is a commercial laboratory. The research team works very close with the medical oncologist and radiologist within the various institutions.

Task 5: Data Entry

All questionnaires have been coded. As women accrue, laboratory and epidemiological data are entered into the software program "Microsoft Excel" for future analyses.

Task 6: Data analysis; Final Report

Data analysis and final report will be completed August 2000.

STATEMENT OF WORK

Tasks	Months	Technical Objectives	Status
1	1-2	Develop and finalize questionnaires for printing.	Completed
2	1-3	Hiring and Training Staff	Completed
3	4-28	Recruitment of cases and controls; informed consent; Data collection	On-going
4	4-30	Send Plasma to Laboratory for analysis; work with Oncologist to determine primary breast cancer cases.	On-going
5	4-30	Data Entry	On-going
6	31-36	Data analysis; Final Report	Not yet Addressed

KEY RESEARCH ACCOMPLISHMENTS

- Finalizing study questionnaires
- Hiring of study personnel
- Enrolling 117 African American women
- On-going data entry

CONCLUSIONS

To date, 117 African American women are enrolled in the study. Recruitment for postmenopausal African-American women with breast cancer is slow because of our exclusion criteria which eliminates women with Type II diabetes and women taking estrogen replacement therapy. However, we have taken the necessary steps to broaden our recruitment efforts. We are currently recruiting at the Georgetown University Medical Center and will start recruiting at the DC General Hospital in October 1999. The PI received approval from DOD for a one-time, no cost extension until August 15, 2000 to complete the study. The extension is needed to successfully complete the project by allowing more time to recruit breast cancer cases.